wherein neural sprouting in said treated tissue is inhibited.

2) (Amended) The method of claim 1 wherein step a) occurs at the same time as said tissue is treated with said clostridial toxin.

3) (Amended) The method of claim 1 wherein step a) occurs prior to treatment of said tissue with said clostridial toxin.

REMARKS

Written Description.

The Examiner has again rejected pending claims 1-6, 9 and 16 as allegedly failing to meet the written description requirement of 35 USC §112(1). Applicants respectfully traverse this rejection.

The Examiner has cited the PTO Final Guidelines on Written Description Requirement, 66 Fed. Reg. 1099 (Jan. 2001) (the "Guidelines") as support for this rejection. The Guidelines make clear that "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." *Id.* at 1105. Such a presumption is present if the invention is either adequately described in the specification or is known to one of ordinary skill in the art. See *id.*

The Examiner has said that the Applicants, in their reply of April 23, 2002, assert that the functional clause added to claim 1 by amendment "sufficiently narrows the scope of the claim so that the written description requirement is met." Actually, this is not an accurate representation of the Applicants' assertion: Applicants merely made the point in the cited statement that the Examiner's grounds for rejection under the written description requirement apply equally to the claim before such amendment; the limitation objected to by the Examiner (the ribozyme or antisense molecule which inhibits expression of CNTF) was present in the originally filed claim. As such, and as stated in the cited Guidelines (66 Fed. Reg. 1099, 1105 (2001)) , the Examiner must overcome the strong presumption that the claim is supported by adequate written description in the specification. As such, the Examiner must establish a *prima facie* case that the claims violate the written description requirement. This fact is not negated by the statement on page 1105, paragraph 2 of the Guidelines, cited by the Examiner.

The Examiner argues that the lack [of literal description?] of appropriate materials for carrying out the invention is properly a written description issue, and then concludes (without analysis) that Applicants were not in possession of the required starting materials (specifically, CNTF inhibitory agents) for practicing the claimed method. Applicants have no opinion concerning the former point in the abstract, and with regard to the presently pending claims Applicants respectfully submit that this point is inapposite.

Applicants do strenuously disagree with the Examiner's conclusion that the claims violate the written description requirement.

To fulfill the written description requirement, a patent specification must allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. *Regents of the University of California v. Eli Lily and Co.*, 43 USPQ2d. 1398, 1404 (Fed. Cir. 1997) (hereinafter "*Lily*"). Although this requirement is sometimes described with reference to the inventor having "possession" of the invention, actual reduction to practice of an invention is only one way in which the requirement may be fulfilled. "Possession" in this context does not mean actual possession of the invention, but rather possession of a mental picture of the invention. *Burroughs Wellcome Co. v. Barr Labs, Inc.*, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994). "Put another way, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding, Inc.*, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (citations omitted). Applicants respectfully submit that the limitation of the method claims currently at issue (e.g., a ribozyme or antisense molecule inhibiting the expression of CNTF) is clearly discerned by the person of ordinary skill in the art.

Almost without exception in the case law addressing the written description requirement the claims at issue are composition claims. Thus, the claimed invention is a tangible material or object, and a written description of such object must necessarily include such limitations as distinguish it from the prior art. The written description so distinguishing the claimed composition must have been made as of the priority date of the patent application so as to inform the public that the inventor had such limitation in mind when the invention was constructively reduced to practice. This is why the Court of Appeals for the Federal Circuit has held "in claims to genetic material . . . a generic statement such as 'vertebrate insulin cDNA,' . . . without more, is not an adequate description of the genus because it does not distinguish from others except by function." *Lily*, 43 USPQ2d at 1406 (emphasis added).

By contrast, the present claims are method claims. Methods are not a tangible object, but rather a means of accomplishing a result. While a definition by function may not suffice to define a composition, a method is a function. In the present case, the Examiner's rejection focuses not on whether the invention is described in accordance with 35 U.S.C. § 112(1), but rather to whether a claim limitation is so described. While Applicants believe the limitation at issue is properly described, the Examiner must consider the claim as a whole when determining if it is patentable. Therefore, while a precise structural description of (for example) an antibody having a given binding specificity may often be necessary to adequately inform the public what was invented if the antibody is the claimed invention, if the invention is instead a therapeutic method, a limitation in the method claim which describes the genus of antibodies having a required affinity, combined with a method for making such antibodies, is therefore patentably precise to

apprise the public what the claimed invention is and that the inventor invented it as of the filing date. This is all the written description requirement requires.

The Guidelines recognize that a functional description may be adequate to patentably describe an invention, even when the invention is a composition:

> Factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Guidelines at 1106.

Thus, both the Guidelines and binding precedent indicate "possession" of a composition can be shown by, among other things, the level of skill in the art and functional characteristics. Obviously such factors would be at least as important when the invention is a method.

The Examiner has stated that because the specification does not disclose a specific ribozyme that inhibits CNTF expression, the claimed method of extending the effective period during which tissue treated with a clostridial toxin is paralyzed is not adequately described. But, as Applicants have repeatedly made clear, Applicants are not claiming a ribozyme or antisense molecule. Applicants are claiming a method of accomplishing a therapeutic effect through the use of any ribozyme or antisense molecule that have the described functional characteristics. Applicants have described how the steps of the method can be carried out; see e.g., at page 22, at Example 3, and in original claim 1.

The Examiner has indicated her belief that the ribozyme of the claim at issue must i) prevent expression of CNTF, ii) must extend the effective period during which tissue treated with a clostridial toxin is paralyzed and iii) must inhibit neural sprouting in the treated tissue. However, steps ii) and iii) are inherent results and/or aims of the Applicants' invention – if the ribozyme is able to prevent expression of CNTF, then it will accomplish results ii) and iii) according to the claimed method.

As stated in the Reply of January 29, 2002 (incorporated herein by reference), the specification includes Usman & Stinchcomb, *Nucl. Acids & Mo. Biol.* 10:143 (1996), which was incorporated by reference. Based upon this disclosure, the remainder of the specification, and the state of the art, a person of skill in the art would immediately know that the present Applicants have invented a method employing a ribozyme which extends the effective period during which tissue treated with a clostridial toxin is paralyzed, as claimed. This reference explicitly describes the optimal size of the ribozyme (about 35

nucleotides; see *id.*, page 244), states that for recognition it requires only the sequence UH (wherein H = A, C or U) immediately 5' to the cleavage site on the target RNA, and states that the sequences in Stems I and III of the stem-loop structure of the ribozyme must be complementary to the substrate sequence adjacent the UH sequence. As stated therein, "This requirement for the base-specific binding of the arms of the ribozyme to the substrate in the motif shown in Fig. 2 is the basis for the rational design of hammerhead ribozymes to any target mRNA containing a UH site. (citation omitted). In any RNA the sequence UH would be expected roughly once every five nucleotides." *Id.* at 245. Thus, given the sequence of the target mRNA (which was published both in print and on line at the filing date of the present application), the person of skill in the art would know that a series of ribozymes directed to different portions CNTF mRNA sequence could easily be constructed and tested for their ability to prevent expression of CNTF.

The Examiner cites *Oka v. Youssefyeh*, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988) for the proposition that conception of a compound requires that the inventor be able to distinguish it from other materials. However, Applicants respectfully believe the Examiner's reliance on *Oka* is misplaced. *Oka* was an appeal of a holding by the Board of Patent Appeals and Interferences in an interference proceeding; the issue (under 35 U.S.C. §102(g)) regarded proof of conception of a claimed chemical compound; the Court of Appeals for the Federal Circuit found that conception of the claimed compound occurred when the inventor possessed an idea of the compound and a method for making the compound. *Oka* did not concern 35 U.S.C. §112(1), the present basis for rejection. Unlike the present claims, *Oka* concerned a claimed composition (compound), rather than a method. In this case, the question is whether on the basis of the disclosure of the patent application and the knowledge of the person of skill in the art, whether the Applicants have distinguished their claimed method from other methods to the person of skill in the art. Applicants emphatically believe they have.

Applicants thank the Examiner for clarifying that the delivery step is not at issue.

Thus, Applicants submit that a person of skill in the art would have immediately discerned the limits of the claims in question, and would have thus been reasonably apprised that the inventor had invented the methods now claimed. For these reasons, Applicants respectfully submit that the Examiner has not met the high burden of establishing a *prima facie* case that the Applicants have not met the written description requirement, and thus request this rejection be reconsidered and withdrawn.

Enablement

The Examiner has also maintained the rejection of claims 1-6, 9 and 16 as allegedly not being

enabled by the specification, for the same reasons advanced in the Office Action dated July 19, 2001. Applicants respectfully traverse this rejection.

The Applicants' arguments in reply to the last Office Action (Reply mailed October 19, 2001) are hereby incorporated by reference in total.

The Examiner argues that the specification lacks sufficient guidance for finding an operative embodiment of an agent able to inhibit expression of CNTF because, although disclosure of methods for making ribozymes is part of the specification and representative CNTF nucleotide sequence(s) were publicly available at the filing date, such information does not teach a person of ordinary skill in the art how to make such an agent without undue experimentation. The Examiner cites Judge Lourie's opinion in *Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d, 1001 (Fed. Cir. 1997) ("*Genentech*") to argue that in this case undue experimentation is required. However, the present specification does explicitly disclose structural requirements for the construction of ribozymes. Such requirements, supplemented with the publicly available nucleotide sequence of various CNTF species, including the human species, and the high level of skill in the art amply disclose to the skilled worker how to make the invention without undue experimentation.

In *Johns Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998) (decided after the *Genentech* case), Judge Lourie, writing for a unanimous three-judge panel, found that the disclosure of methods of making antibodies, combined with the disclosure of a single antibody species, did not even raise a material issue of fact concerning the enablement of composition claims drawn to the entire genus of antibodies binding to a specific antigen. Despite the fact that the evidence included an expert declaration that the amount of work necessary to produce these antibodies was more difficult than to produce other antibodies, the court said that such evidence only suggested that the technique was not foolproof and that success with this technique commonly required repetition. The court stated "This lack of certainty was thus not attributable to a failure of disclosure," *id.* at 1719, and that to make the genus of antibodies in light of the specification might require considerable work, but did not constitute undue experimentation.

In the present case, methods are claimed. The patent application discloses in the material incorporated by reference that ribozymes require certain secondary structural characteristics, and gives examples of them (see Usman et al.). For example, hammerhead ribozymes are the "clear favorite for exogenous ribozymes delivery" because of their small size and minimal substrate requirements. Usman at 244. The nucleotide sequence requirements for the catalytic core of a hammerhead ribozyme are shown in Fig 2 of Usman, page 245, and the residues of Stem I and resides of Stem III constituting the targeting or "external guide" sequence. The use and location in the molecule of 2' modifies sugars, particularly 2'alkoxy residues, to increase nuclease resistance is disclosed at page 247. Synthesis of RNA was at the

time of filing this application a matter of routine – even in 1996 the time of synthesis and deprotection of a 36-mer ribozyme was about 6 hours. *Id.* At 250.

Regarding the selection of a CNTF mRNA target site against which to design a ribosome, this again is a matter of routine for which guidance is provided in the specification. The cleavage site is ubiquitous, consisting of the UH (H=A,C or U) dimer. Stems I and III must be synthesized to hybridize of either side of the UH residue. The specification states that one can synthesize ribosomes directed against several potential cleavage sites and measure their ability to cleave the mRNA substrate. Alternatively, according to the specification, one can find accessible sites on the target mRNA by constructing a series of short deoxynucelotides complementary to different segments of the mRNA and allowing them to hybridize to the target mRNA. Addition of RNAse H (which cleaves RNA:DNA duplexes) to the hybridization mixture and detection of cleavage indicates that the target sites are accessible to the hammerhead ribosyme. See *id.* at 250-251. A third option is to synthesize a series of ribozymes directed to different target sequences containing a UH residue at their center. See *id.* Thus, all of this disclosure is found in the specification.

The Examiner has contended that the present application only discloses what is intended to be done and how it is intended to work. Actually, the specification does much more than that. It teaches that by following the ribozyme design criteria disclosed in the specification, and by obtaining the nucleotide sequence of CNTF (published and obtainable by the person of ordinary skill in the art within seconds on the Internet from , e.g., the National Center for Biotechnological Information via the Internet) one can make the ribozymes used in the claimed methods. The fact that some routine selection of optimal ribozymes may be necessary does not constitute undue experimentation any more than the making, screening and selection of antibodies did in the *Johns Hopkins* case.

The Examiner alleges a new enablement issue based on Applicant's addition of subparagraphs and headings to claim 1. The Examiner states that the "wherein" clause of step a) should follow steps a) and b) because the specification teaches that neural sprouting is only inhibited after administration of the clostridial toxin. Applicants are unable to find this teaching in the specification; nevertheless, Applicant agrees that the "wherein" clause will be moved to the end of the claim, since the claimed method requires both steps.

Thus, the specification provides ample examples of how to make the agents to be used in the claimed methods, and Applicants respectfully request that the Examiner reconsider and withdraw this ground for rejection.

Indefiniteness

The Examiner has alleged that claims 1-6, 9 and 16 as allegedly indefinite. Applicants traverse this rejection.

Claims 2 and 3 have been amended to replace "said contacting step" with "step a)". Applicants thank the Examiner for pointing out this ambiguity, which has now been corrected.

Claims 1-6, 9 and 16 are said to be indefinite because the claims encompass non-elected subject matter present in claim 1. However, in the communication dated April 17, 2001 the Applicants elected to prosecute Examiner's Restriction Group III, drawn to methods for extending the effective time tissue is paralyzed by a clostridial toxin comprising administering agents that prevent the expression of various neurotrophic factors. Applicants were also requested to elect a species of such agent; Applicants elected CNTF as such species.

Applicants therefore have elected an invention to prosecute and claim 1 is directed thereto, as a generic claim linking species. See MPEP 809.02. While Applicants have further elected the species of methods employing agents blocking expression of CNTF, 37 CFR §1.141 permits the inclusion of more than one species in a single application when it is found that a generic claim is allowable. Clearly, the generic linking claim must be present in the application during prosecution even after the election of species is made. MPEP 809.04 states that when the requirement for restriction is predicated on the non-allowability of a linking claims, Applicants have the right to retain claims directed to non-elected subject matter. For this reason, Applicant respectfully disagrees that the retention of Claim 1 is improper.

The Examiner also claims that the term "neural sprouting" is indefinite. But the specification describes sprouting as the production of recent synaptically active processes at the neuromuscular junction. E.g., Specification at 6, lines 11-17. "Production" is defined as the progress or advance of something (Webster's New American Dictionary 1995); and thus the term "neural sprouting" encompasses the progress of and both: a) the appearance and b) the continued growth of such processes. This meaning is therefore definite to the person of skill in the art.

CONCLUSION

For the reasons indicated above, Applicants respectfully urge the Examiner to reconsider and withdraw the standing rejections. While no fee is thought to be required with regard to this communication, if Applicants are in error please use our Deposit Account 01-0885 for the payment of any fees that may be due.

Respectfully Submitted,

Date: 8/16/02

Signature: _____

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MARKED-UP VERSION OF AMENDED CLAIMS

2. (Thrice Amended) A method for extending the effective period during which tissue treated with a clostridial toxin is paralyzed comprising:

c) contacting said tissue with a composition comprising an agent able to prevent the expression of a polypeptide selected from the group consisting of: IGF I, IGF II, cilary neurotrophic factor, NT-3, NT-4, brain-derived neurotrophic factor, leukemia inhibitory factor, tenascin-C, ninjurin, neural cell adhesion molecule, and neural agrin, [wherein neural sprouting in said treated tissue is inhibited], and

d) contacting said tissue with a clostridial neurotoxin,

wherein neural sprouting in said treated tissue is inhibited.

2) (Amended) The method of claim 1 wherein [said contacting] step a) occurs at the same time as said tissue is treated with said clostridial toxin.

3) (Amended) The method of claim 1 wherein [said contacting] step a) occurs prior to treatment of said tissue with said clostridial toxin.